Endoscopic Ultrasound–guided Fine-Needle Aspiration of a Portal Vein Thrombus to Aid in the Diagnosis and Staging of Hepatocellular Carcinoma

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The most common primary tumor of the liver is hepatocellular carcinoma (HCC), also known as hepatoma.[1] There are several risk factors for developing hepatoma, such as chronic hepatitis B and C virus infection, cirrhosis, and carcinogens (ie, aflatoxin).[2] The incidence of HCC, which is often a fatal disease, is on the rise in developed nations, including the United States. Over the past 3 decades, the incidence of HCC has not only increased, but has also shifted toward younger individuals.[3]

The stage of HCC at diagnosis is an important factor in overall treatment course and prognosis. Patients with early-stage disease can be offered possible curative surgical intervention, transplantation, or resection. In contrast, an advanced disease stage negates any surgical intervention, and only palliative treatment, such as chemotherapy or chemoembolization, can be offered to these patients. Therefore, every possible attempt should be made to accurately stage HCC. Fine-needle aspiration (FNA) of a portal vein thrombus (PVT), when present, is an effective procedure for diagnosing and staging HCC.[4-9] Although percutaneous ultrasound (US)-guided FNA of a PVT has been well documented, we are only aware of 1 case report in the literature that has reported the use of endoscopic ultrasound (EUS)-guided FNA of a PVT to diagnose HCC.[4-10] We report the second case of EUS-guided FNA of a PVT in a patient without any history of cirrhosis to successfully diagnose and stage HCC in the absence of a liver mass on abdominal computed tomography (CT) and US.

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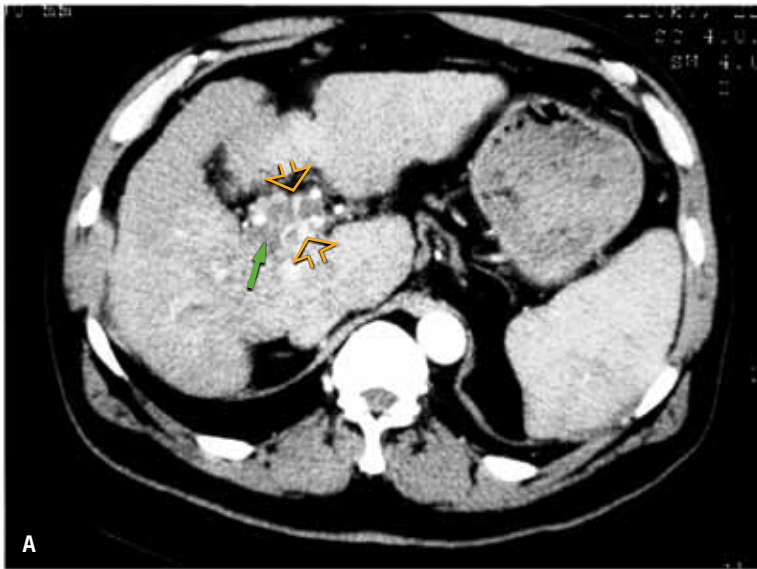
Case Report

A 53-year-old man with a history of noninsulin-dependent diabetes mellitus presented with a 2-month history of fatigue, intermittent right-sided abdominal pain, and decreased appetite. He had no history of weight loss, jaundice, liver disease, or alcohol abuse. An abdominal examination was essentially normal, and no evidence of chronic liver disease was seen on a general examination. His laboratory studies were remarkable for an alkaline phosphatase level of 231 U/L (normal, 38–112 U/L), alanine aminotransferase of 78 U/L (normal, 27–65 U/L), aspartate aminotransferase of 86 U/L (normal, 13–39 U/L), and a platelet count of 97,000 cells/mm^3 (normal, 130,000–400,000 cells/mm^3). The patient's alpha-fetoprotein level was markedly elevated at 1,448 ng/mL (normal, 1–9 ng/mL). His total and direct bilirubin levels were within normal ranges.

An abdominal CT revealed a cirrhotic liver and PVT. Enhancement of the PVT during the arterial phase raised a strong suspicion of tumor thrombus (Figure 1). No definite hepatic mass was seen, but the presence of an enhancing PVT, along with a markedly elevated alpha-fetoprotein level in the absence of any other etiology, was highly suggestive of an occult HCC.

An EUS was performed using a linear-array echoendoscope (UCT-140, Olympus America) while the patient was under deep sedation with propofol. The liver was diffusely heterogeneous without a focal hepatic mass. A hypoechoic lesion measuring 1.9 cm × 1.9 cm was noted in the lumen of the main portal vein (Figure 2A). On power-flow Doppler, no flow was seen in the portal vein. Multiple periportal vein, serpiginous, anechoic structures with flow were noted on color Doppler, which was consistent with neovascularization.
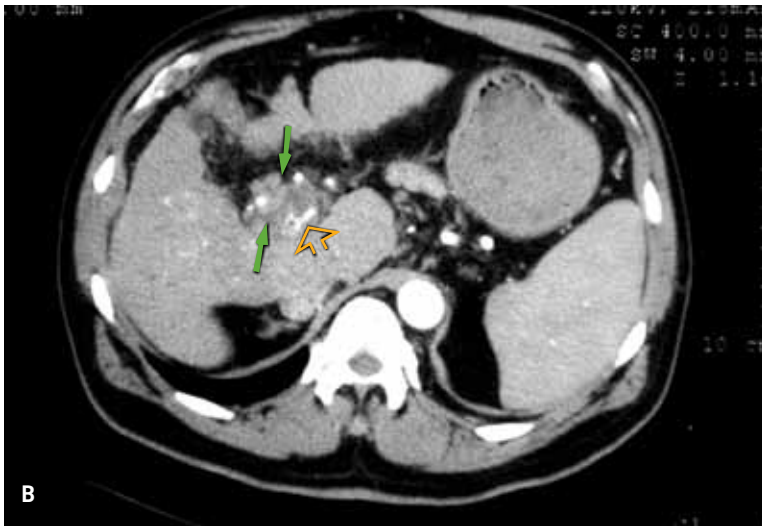
Figure 1. Arterial-phase axial abdominal computed tomography (CT) images showing cirrhosis, with prominence of the lateral segment of the left hepatic lobe and caudate. There is expansion of the central portion of the central vein (green arrows), which is arterialized (orange arrows) with enhancing and tortuous vessels. Figure 1B is at a slightly lower level than Figure 1A. Although no hepatic mass is identified, these CT findings are highly consistent with tumoral thrombus from hepatocellular carcinoma.

EUS-guided FNA was performed on the PVT using a 25-gauge needle (EchoTip Ultrasound Needle, Wilson-Cook Medical, Inc.) over a total of 4 passes (Figure 2B). Every effort was made during the FNA session to avoid the vasculature and common bile duct. Due to the setup in our endoscopy unit, a cytopathologist was not present during the FNA session. The patient tolerated the procedure well, without any immediate or delayed complications.

Cytopathologic examinations and immunohistochemical stainings of the specimen revealed malignant cells consistent with poorly differentiated HCC (Figure 3). Subsequently, liver, spleen, and gallium scans were performed; their findings were consistent with HCC in the right hepatic lobe.

The patient died within months from HCC-related complications.

Discussion

HCC accounts for approximately 90% of primary liver cancers and causes at least 1 million deaths each year worldwide.[11] A marked increase in the incidence of HCC has been noted in developed countries since the 1990s, which has been attributed to the effects of chronic hepatitis B and C virus infection.[2] Tsukuma and associates showed that patients infected with hepatitis B surface antigen have an approximately 7-fold increased risk of HCC, and patients with hepatitis C antibody have a 4-fold increased risk.[12]

Figure 2. Endoscopic ultrasound (EUS) image of a lesion occupying nearly the entire lumen of the portal vein, with multiple collateral vessels present **(A)**. EUS-guided fine-needle aspiration of the portal vein thrombus **(B)**.

Noninvasive radiologic imaging modalities, such as CT, US, and magnetic resonance imaging (MRI), can be used to diagnose HCC, though there are limitations to the accuracy of these techniques when diagnoses are made without tissue sampling. Three main growth patterns determine the imaging appearance of HCC: diffuse infiltrative, solitary massive, and multinodular.[11,13] The most difficult pattern to detect, particularly in the face of underlying parenchymal liver disease and cirrhosis, is the diffuse infiltrative pattern, which is the pattern seen in our patient.[11,13] Lesions are typically hypervascular on contrast-enhanced CT and show prominent enhancement on arterial-phase images, with subsequent washout on delayed-phase images.[11,13] Vascularity of HCC can be assessed by various methods, including US with Doppler,

contrast-enhanced CT, and contrast-enhanced MRI. Angiography and, more recently, EUS with Doppler can also be used. The various types of traditional angiography are invasive; due to advances in other imaging techniques in recent years, however, they are rarely required. The vascular pattern of a liver mass suggests, but may not be entirely diagnostic of, HCC.

On US, HCC has variable and relatively nonspecific appearances: hypoechogenicity, mixed echogenicity, or hyperechogenicity. This variability causes the wide range of sensitivity (20–96%) reported with US for the diagnosis of HCC.[10,11] Hyperechogenicity can result from calcification, hemorrhage, and the well-known phenomenon of fatty metamorphosis associated with HCC.[11] Therefore, it is not surprising that CT, US, and EUS failed to reveal
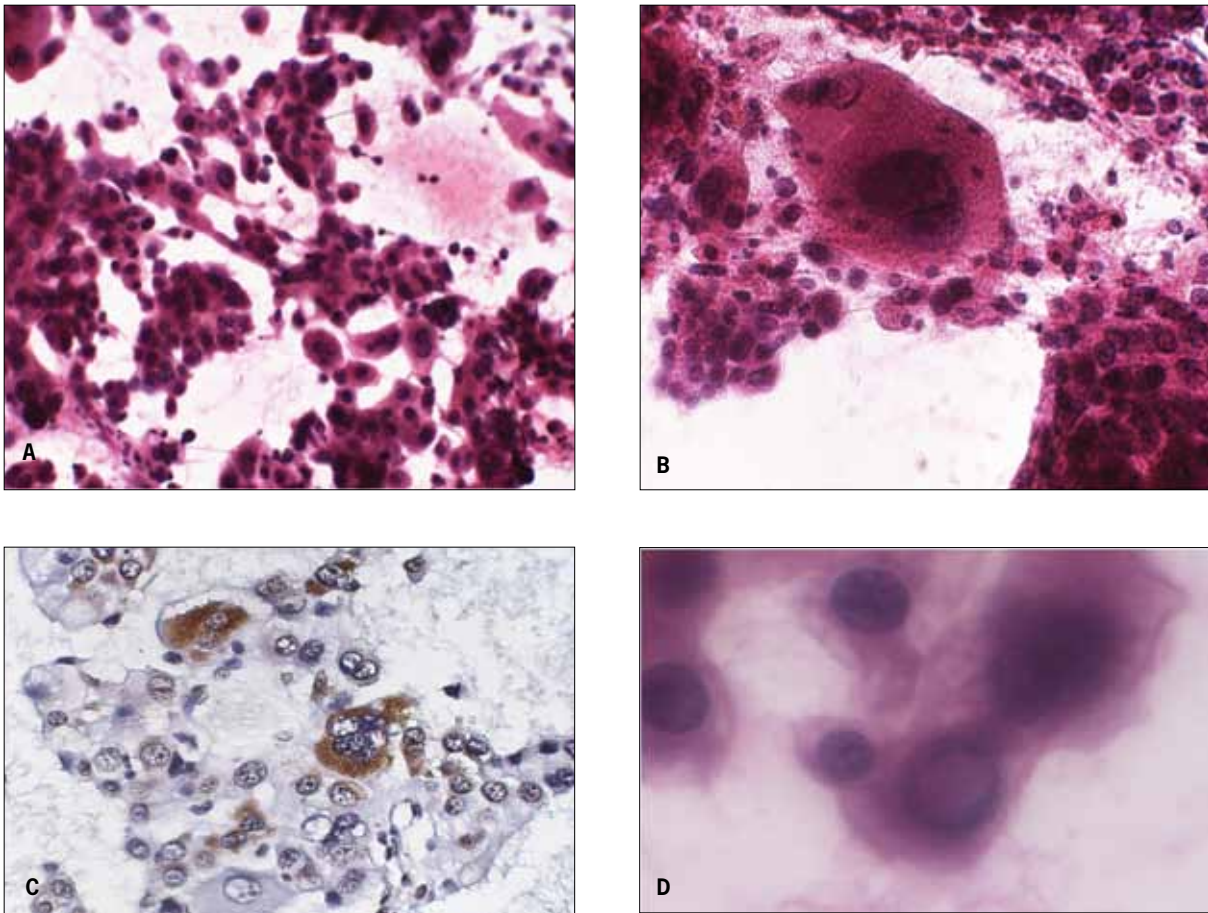
Figure 3. A hypercellular tumor in the portal vein exhibiting abundant eosinophilic cytoplasm, marked cellular pleomorphism, and dyscohesion of tumor cells (hematoxylin and eosin stain, 200× magnification; **A**). Intranuclear cytoplasmic inclusion in hepatocellular carcinoma (hematoxylin and eosin stain, 600× magnification; **B**). Immunoperoxidase stain for Hep Par 1, a marker for hepatocyte lineage, is positive in the cytoplasm of the tumor cell (400× magnification; **C**). A bizarre, multinucleated tumor giant cell (hematoxylin and eosin stain, 600× magnification; **D**).

a liver mass in our patient. Of note, EUS can be used to visualize the left hepatic lobe much better than the right hepatic lobe; therefore, it is not uncommon to miss a lesion in the right hepatic lobe on EUS.

HCC has several characteristic findings, including invasion of the tumor into the portal and hepatic veins. Invasion of the portal vein, either by direct extension or metastasis, is common and has been reported in up to 72% of patients with HCC.[6,14,15] This rate is much higher than the rate of portal vein thrombosis in the setting of cirrhosis uncomplicated by HCC (1–5.7%).[15]

Portal vein tumor thrombosis (PVTT) on imaging studies appears as a low-density plug within a dilated main or lobar portal vein.[1] This plug enhances with contrast in the arterial phase on both CT and MRI, as in our patient, and may have arterial signal on Doppler US. Nontumor portal vein thrombosis has a similar appearance to PVTT; however, it does not enhance with contrast nor does it have any Doppler signal. Therefore, whenever a PVT enhances with contrast or has a Doppler signal, PVTT remains the diagnosis until proven otherwise. Of the many complications of HCC, PVTT is among the most dreaded, as it has poor prognostic indicators and precludes resection or liver transplantation.[9] Since not every PVT in a patient with HCC is a tumor thrombus and since the nature of the thrombus will ultimately determine the course of treatment, in our opinion, every effort should be made to distinguish between a tumor and a nontumor PVT.[5] In addition, PVTT does not always demonstrate neovascularity, which makes FNA of a PVT necessary in order to stage a known HCC. Studies have shown that US-guided FNA is effective in the initial diagnosis of HCC, even when

imaging techniques fail to detect liver changes compatible with HCC or when biopsy of the liver lesion fails to diagnose HCC. [4,6-8]

Multiple case reports and case series have demonstrated the safety and efficacy of FNA in the diagnosis and staging of HCC. [4-9] The vast majority of the published literature describes percutaneous US-guided FNA of a PVT, with only 1 report noting the use of EUS-guided FNA of a PVT in a single patient. [4-9] Despite these reports, US-guided FNA of a PVT has not become a widely performed procedure, to our knowledge, and it is not routinely available at many institutions beyond liver transplant centers. The reasons for this lack of availability are not clear and may be due to inadequate numbers of well-trained interventional radiologists or the fear of possible complications, particularly bile duct or vascular injury (which could lead to potential biliary peritonitis or pseudoaneurysm formation) and various bleeding complications. [5] Another challenge with US-guided FNA of a PVT is the difficulty of sampling a thrombus located in the central main portal vein while avoiding the inclusion of any normal hepatocytes or associated liver masses. In a series of 18 patients who underwent US-guided FNA of a PVT, hepatocytes were evident in 17%, which may confuse the clinical picture and impose substantial difficulty on the cytopathologist when distinguishing between normal hepatocytes and well-differentiated HCC. [9] EUS-guided FNA can be performed with relative ease (and without the need for a transhepatic approach) either through the gastric wall from the portal vein confluence or transduodenally from the duodenal bulb or second portion, where the entire portal vein can be visualized from the confluence into the porta hepatis. Therefore, the presence of any hepatocytes in specimens obtained via EUS-guided FNA will suffice for diagnosis of HCC (even well-differentiated HCC).

It may be argued that when a liver mass and a PVT coexist, tissue sampling of the PVT is preferred in order to avoid difficulty in diagnosing well-differentiated HCC as well as to simultaneously provide accurate staging information. In addition, due to the proximity of the echoendoscope to the portal vein and the ability to readily identify adjacent structures, the FNA needle can be positioned directly into the PVT, completely avoiding the common bile duct and vasculature, particularly collateral vessels. Therefore, at least theoretically, complications can be minimized. Another advantage of EUS-guided FNA over percutaneous US- or CT-guided FNA, in general, is a lower potential for needle tract seeding. To our knowledge, only 2 cases in the literature have reported needle tract seeding with EUS-guided FNA, the first case in a patient with melanoma and the second case in a patient

with pancreatic adenocarcinoma. [16,17] There are also data suggesting a lower incidence of peritoneal carcinomatosis with EUS-guided FNA compared to percutaneous FNA. [18] In contrast, an advantage of percutaneous FNA over EUS-guided FNA is that the former procedure can be performed with local anesthesia in the majority of cases, thereby avoiding the need for conscious or deep sedation and associated complications. However, it is well documented in the literature that EUS (including EUS-guided FNA) with sedation is an extremely safe procedure with a very low serious complication rate.

In summary, we report the second case, to our knowledge, of EUS-guided FNA of a PVT for the diagnosis and staging of HCC that was not evident on abdominal CT or US. The ease, safety, and efficacy of this evolving technique, along with its expanding clinical applications, was demonstrated once again. We believe that EUS-guided FNA should be utilized more frequently to diagnose the etiology of portal vein thrombosis and to stage HCC.

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Review
Utility and Safety of EUS-guided Portal Vein FNA

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Hepatocellular carcinoma (HCC) is a fatal complication of cirrhosis; however, recent treatment advancements, including liver transplantation in select cases, have made HCC a potentially curable disease. Curative treatment options are attempted only in the absence of extensive vascular invasion or extrahepatic spread. The diagnosis of HCC is usually established by radiologic imaging, as the laboratory tests currently available have inadequate sensitivity or specificity. However, an elevated alpha-fetoprotein (AFP) level (>200 ng/mL), or a rising AFP level, in the presence of a mass on imaging has a very high positive predictive value for the diagnosis of HCC. Simi-larly, a significant elevation in AFP level (>1,000 ng/mL), in the absence of a testicular tumor, is highly suggestive of an occult HCC, particularly in the presence of cirrhosis, even in the absence of a visible lesion on sensitive imaging modalities, such as triple-phase computed tomography (CT) scan or contrast-enhanced magnetic resonance imaging (MRI). For this reason, AFP is still used in many centers as a complementary test for both surveillance and diagnosis of HCC, despite its limitations.

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Imaging modalities, such as transabdominal ultra-sound (TA-US), CT scan, or MRI, have variable sensitivi-ties and specificities for the diagnosis of HCC in patients with cirrhosis, depending on the technique and expertise of the operator and radiologist. Our group has previously evaluated the potential role and limitations of endoscopic ultrasound (EUS) for the diagnosis of HCC.[1,2] Based upon the published data, we have suggested that EUS and EUS-guided fine-needle aspiration (FNA) may be par-ticularly useful in the management of a subset of patients with small liver lesions that are difficult to sample via traditional TA-US and lesions located in liver segments that can be adequately visualized by EUS.

The case report presented by Michael and associates illustrates the difficulties of diagnosing and staging HCC in the absence of a clearly defined primary liver mass.[3] The patient described in this case report had no clinical signs or history of chronic liver disease and presented with a markedly elevated AFP level (1,448 ng/mL). His CT scan showed cirrhosis and a dilated, thrombosed portal vein (PV). There was no obvious liver mass on the CT scan, but there was arterial enhancement of a PV thrombus, raising a strong suspicion of a tumor throm-bus. The diagnosis was made through EUS-guided FNA of the PV thrombus, which revealed a poorly differenti-ated HCC.

As Michael and coworkers pointed out, PV thrombo-sis (PVT) is a common finding in patients with advanced cirrhosis, due to either sluggish or turbulent blood flow and/or clotting abnormalities.[3] Tumor thrombus, unlike nontumor PVT, shows arterial enhancement on CT or MRI. The diagnosis of a tumor thrombus is relatively easy when patients present with a liver mass suggestive of HCC and PV thrombus that enhances on arterial phase of CT or MRI. However, the diagnosis of tumor throm-bosis is difficult in the absence of a discrete or infiltrating liver mass or when there is nondiagnostic elevation of AFP level or equivocal enhancement of tumor thrombus. When liver transplantation or a curative resection is planned, a firm diagnosis or exclusion of tumor thrombus becomes critically important.

Figure 1. Endoscopic ultrasound–guided angiography of the portal vein.

This case report raises several clinically important issues, including the utility and safety of FNA of the PV.[3] Earlier attempts at this procedure, performed under TA-US to diagnose suspected HCC thrombus, were reported from 1992 to 1997.[4-12] These studies clearly demonstrated the effectiveness of FNA of the PV. In the largest reported series, only 6 aspirates (12.5%) were negative for malignancy, 39 aspirates were positive (81.3%), and 3 aspirates were suspicious for malignancy (6.2%).[8] Despite the effectiveness and safety margins found in these reports, there was a paucity of published studies on TA-US–guided FNA of the PV after these initial publications. There could be many reasons why this highly effective and seemingly safe technique has not become a standard option in the diagnosis and staging of HCC in patients with suspected tumor thrombus of the PV. One reason could be the improvement in CT and MRI, which makes tissue sampling unnecessary in most patients. Another reason could be the technical difficulties of TA-US–guided aspiration in patients with cirrhosis, obesity, or ascites. Spatial resolution of the ultrasound beam is directly proportional to its frequency, but the penetrating ability of the ultrasound beam is inversely proportional to its frequency. During evaluation of the liver and PV with TA-US, the ultrasound beam has to travel at least 20–25 cm before reaching the PV. In this situation, only a relatively low frequency (3.5 mHz) ultrasound beam could be used, making evaluation and precise targeting of the PV difficult and thereby increasing the potential for complications (inadvertent injury to adjacent bile ducts, arterial vessels, and so on). In addition, during the percu-
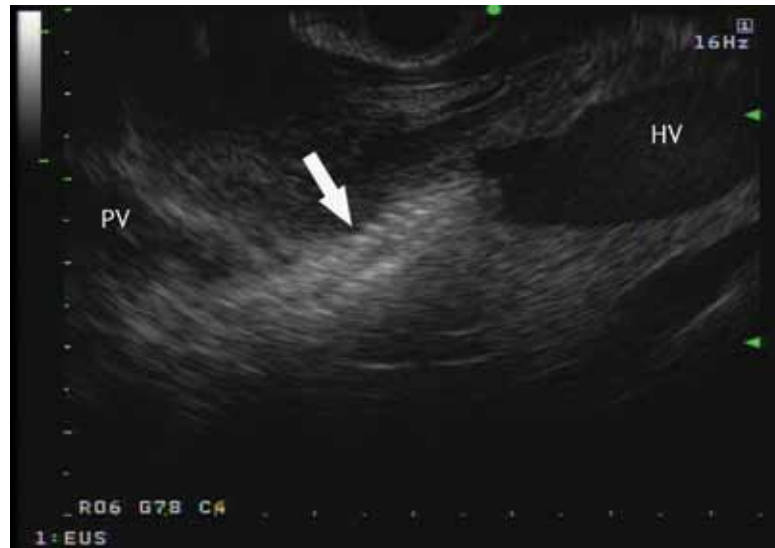
taneous approach, the needle also has to travel a relatively long distance from the skin to the PV through a cirrhotic liver. Perhaps for all of these reasons, TA-US–guided FNA of the PV has not become more widely used.

In 2004, Lai and colleagues published the first case report of EUS-guided FNA of the PV for diagnosis of HCC, which was followed by a second report in 2007 by Storch and coworkers.[13,14] EUS-guided FNA of the PV has undeniable advantages over TA-US. An echoendoscope can deliver the source of the ultrasound beam within 2–3 cm of the PV, uses high frequency (10–12 mHz) ultrasound, and provides excellent resolution and reliable visualization of the PV, its content, and surrounding tissue and organs. Moreover, the FNA needle has to travel only a short distance, making the procedure quick and precise. The case report presented by Michael and associates confirms the previous observations regarding the ease, safety, and efficacy of EUS-guided FNA for suspected tumor thrombus of the PV and strongly advocates its use for HCC diagnosis and staging.[3]

EUS-guided intravascular procedures have even more potential than aspiration of cytologic material from a thrombosed PV. Recent animal experiments and human studies have demonstrated successful use of EUS as a platform for various diagnostic and therapeutic intravascular interventions: EUS-guided angiography, PV catheterization and pressure measurements, and even EUS-guided creation of an intrahepatic portosystemic shunt and embolization of gastric varices (Figures 1 and 2).[15-20] Although interventional EUS remains in an early stage of development, it could become a valuable clinical tool in the management of patients with cirrhosis, portal hypertension, HCC, and other liver diseases.

Although the 3 case reports describing EUS-guided FNA of a PVT demonstrated the efficacy and safety of the procedure, numerous technical questions remain unanswered: Could contamination of the FNA needle with gastric and/or duodenal cells lead to misinterpretation and false-positive results? Could the tumor spread through the FNA needle track? It could be argued that this risk is perhaps not clinically relevant in an individual with a tumor thrombus in the PV. Finally, and, most importantly, how high is the risk of bleeding after puncture of the thrombosed PV with an FNA needle? Carefully managed, large, prospective clinical studies are needed to answer all of these questions before EUS-guided FNA of the PVT can be recommended as a routine test in patients with HCC and suspected malignant PVT. Despite these concerns, we believe that EUS-guided FNA of the PV should be considered when a firm diagnosis or exclusion of PV tumor thrombus is critically important, as when curative options are potentially available.

Figure 2. Endoscopic ultrasound (EUS)-guided creation of an intrahepatic portosystemic shunt (arrow). The proximal end of the newly created shunt is inside the hepatic vein (HV), and the distal end is inside the portal vein (PV).

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